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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/385,114	08/27/99	WHITEHOUSE	M	1543.004/121

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CHIRON CORPORATION
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EXAMINER	
ROBINSON,H	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 09/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/385,114	Whitehouse
Examiner	**Art Unit**
Hope Robinson	1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 18, 2000* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *10-67* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *10-67* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Applicant's response to the Office Action mailed December 4, 2000 in Paper No. 17 on June 4, 2001 is acknowledged.

2. Claims 1-9 have been canceled. Claims 10, 13, 15, 17, 22, 23, 26, 30, 33, and 35 have been amended. Claims 38-67 have been added. Claims 10-67 are pending.

3. The rejections under 35 U.S.C. 102(b) have been withdrawn.

4. The following grounds of rejection remain or are applicable:

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 is indefinite because the claim lacks antecedent basis for the recitation of SEQ ID NO: 2 which is not recited in the independent claim.

Claim Rejections - 35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 10-67 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Franco (U.S. Patent No. 4,378,347, March 29, 1983) in view of Sellke et al. (The Society of Thoracic Surgeons, vol. 65, pages 1540-1544, 1998) and Uchida et al. (American Heart Journal, vol. 130, no. 6, pages 1182-1188, December 1995) based on an angiogenically active fragment or mutein thereof.

Franco disclose a method and use of an effective dose of FGF for treatment of myocardial infarct and heart surgery procedures such as coronary bypass operations. Franco disclose that the

preferred dosage is about 10μg to 1 gram of FGF per 100 grams of heart which is directly injected into the heart. Franco do not explicitly teach the sequence contained in SEQ ID NO: 2. However, Sellke teach the sequence contained in SEQ ID NO: 2 and a method for treating human patients for coronary artery disease (see page 1541, col. 1) comprising administering recombinant human b-FGF also known as FGF-2, to one or more coronary vessels (see Figure 1).

Sellke also teach the use of therapeutic angiogenesis using naked DNA plasmids encoding angiogenic growth factors, DNA delivered by an adenoviral or liposomal vector, or the administration of authentic growth factor proteins to improve perfusion in ischemic regions of myocardium and in patients with peripheral vascular disease. Furthermore, Sellke teach that the delivery of the protein as opposed to the DNA encoding the protein has a potential advantage of simplicity, consistent delivery and safety. In addition, Sellke teach that basic fibroblast growth factor (bFGF) has both angiogenic and mitogenic potential. In addition, Sellke teaches that the angiogenic effect of bFGF is dose dependent and demonstrates the safety and technical feasibility of therapeutic angiogenesis with basic fibroblast growth factor. Additionally, Sellke teach a dose of bFGF that falls within the range recited in claims 1 and 10. Sellke further teaches that the patients were heparinized prior to cardiopulmonary bypass surgery and the administration of bFGF (see pages 1540-1543).

In-so-far-as Sellke does not teach administration into a peripheral vein, Uchida teaches that intracoronary injection of bFGF in dogs resulted in a significant increase in the number of collateral vessels and subsequent salvage of the infarcted myocardium (with heparin sulfate).

Uchida assert that FGFs act as regulatory proteins that induce the proliferation of a variety of cells and function as an angiogenic factor in vitro and in vivo. Furthermore, Uchida teach a method to administer bFGF selectively and safely into the infarcted area, irrespective of the coronary anatomy and contraindications for coronary interventions and that this method can be widely applied as a therapeutic regimen for myocardial salvage to the patients with acute myocardial infarction or as a preventive regimen for myocardial infarction.

Therefore, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention as a whole by combining the teachings of the above references because Franco, Sellke and Uchida teach a composition for inducing angiogenesis, the sequence contained in SEQ ID NO: 2 with a high sequence identity and a unit dose that falls within the claimed dosage range. In addition, Sellke disclose the benefits of using bFGF.

Furthermore, Uchida disclose that in patients bFGF injected into the coronary artery may not reach the infarcted area, because it may be conjugated with the extracelluar matrix at the site of coronary lesion or may enhance stenosis. Therefore, by administration of bFGF selectively and safely into the infarcted area, irrespective of the coronary anatomy and contraindications for coronary interventions, this method can be widely applied as a therapeutic regimen (see page 1182). One of ordinary skill in the art would be motivated to produce a unit dose composition to be delivered in these areas for treatment of coronary artery disease and myocardial infarction as taught by Franco and Sellke because of the benefits described by Sellke and Uchida. Thus, the

claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

7. Applicant's response filed on June 4, 2001 in Paper No.17 has been fully considered. Applicant's response was sufficient to over come the rejections under 35 U.S.C. 102(b), however, the rejection under 35 U.S.C. 103(a) remains. The response on page 12 agrees that the reference by Franco demonstrates myocardial injection of bFGF to obtain beneficial reduction in infarct size. However, applicant argues that the reference fails to demonstrate safety and or efficacy in either animal model disclosed. However, efficacy is not at issue because a mere teaching or suggestion of the claimed method is all that is required to render the invention as obvious. Furthermore, applicant also agree that the reference by Uchida teach intracoronary injection of bFGF which resulted in significant increase in the number of collateral vessels and subsequent salvage of the infarcted myocardium. However, applicant contends that the reference teaches away from the claimed invention by outlining drawbacks to this type of therapy. Applicant's argument is limited because the reference further teaches that this method can be widely applied as a therapeutic regimen for myocardial salvage or as a preventive regimen for myocardial infarction. Again a mere teaching or suggestion is the only requirement for obviousness. Applicant argues that the Sellke reference doesn't teach the route of administration used in the claimed invention, however, Sellke teaches the claimed sequence and a method for treating coronary artery disease and the reference is applied in combination with the Franco and Uchida references. In addition, the claims

are directed to "angiogenically active fragment or mutein thereof" which is taught by the combined teachings of the references. Thus, the combined teachings of the above references renders the claimed invention as obvious because an angiogenically active fragment is taught and the sequence in association with a medicament as claimed. Therefore, the rejection has been maintained.

Note also that the new grounds of rejection instituted under 35 U.S.C. 112, second paragraph is due to applicant's amendments to the claims.

Conclusion

8. Applicant's amendment necessitated the new/modified ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope Robinson whose telephone number is (703) 308-6231. The examiner can normally be reached on Monday and Wednesday-Friday from 9:00 am to 5:30 pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S.F. Low, can be reached at (703) 308-2923.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. The official fax phone number for Technology Center 1600 is (703) 308-4242. Please affix the examiner's name on a cover sheet attached to your communication should you choose to fax your response. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

Karen Cochran-Carlson PhD

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER

Hope Robinson, MS

Patent Examiner